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(71) Applicant(s)

Merck & Co Inc

(Incorporated in USA - New Jersey)

PO Box 2000, Rahway, New Jersey, 07065-0900,
United States of America

(56) Documents Cited

WO 95/13799 A1 WO 95/11009 A1

Proc. Int. Symp. Controlled Bioact. Mater. Vol. 23 1996
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(58) Field of Search

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(72) Inventor(s)

Rey T Chern

James C Tang

Roger A Wilson

(74) Agent and/or Address for Service

W G Cole

Merck & Co Inc, European Patent Department,
Terlings Park, Eastwick Road, HARLOW, Essex,
CM20 2QR, United Kingdom

(54) Process for removing an organic solvent from lactide-glycoside copolymer microspheres

(57) Polylactide-co-glycoside (PLGA) and a lipophilic drug, such as avermectins, are emulsified in a two phase oil-in-water system, wherein the organic phase solvent is ethyl acetate. Preferably the aqueous phase is polyvinyl alcohol. The microsphere emulsion is introduced immediately into a water reservoir to wash away the ethyl acetate. The resulting microspheres are then dried in nitrogen.

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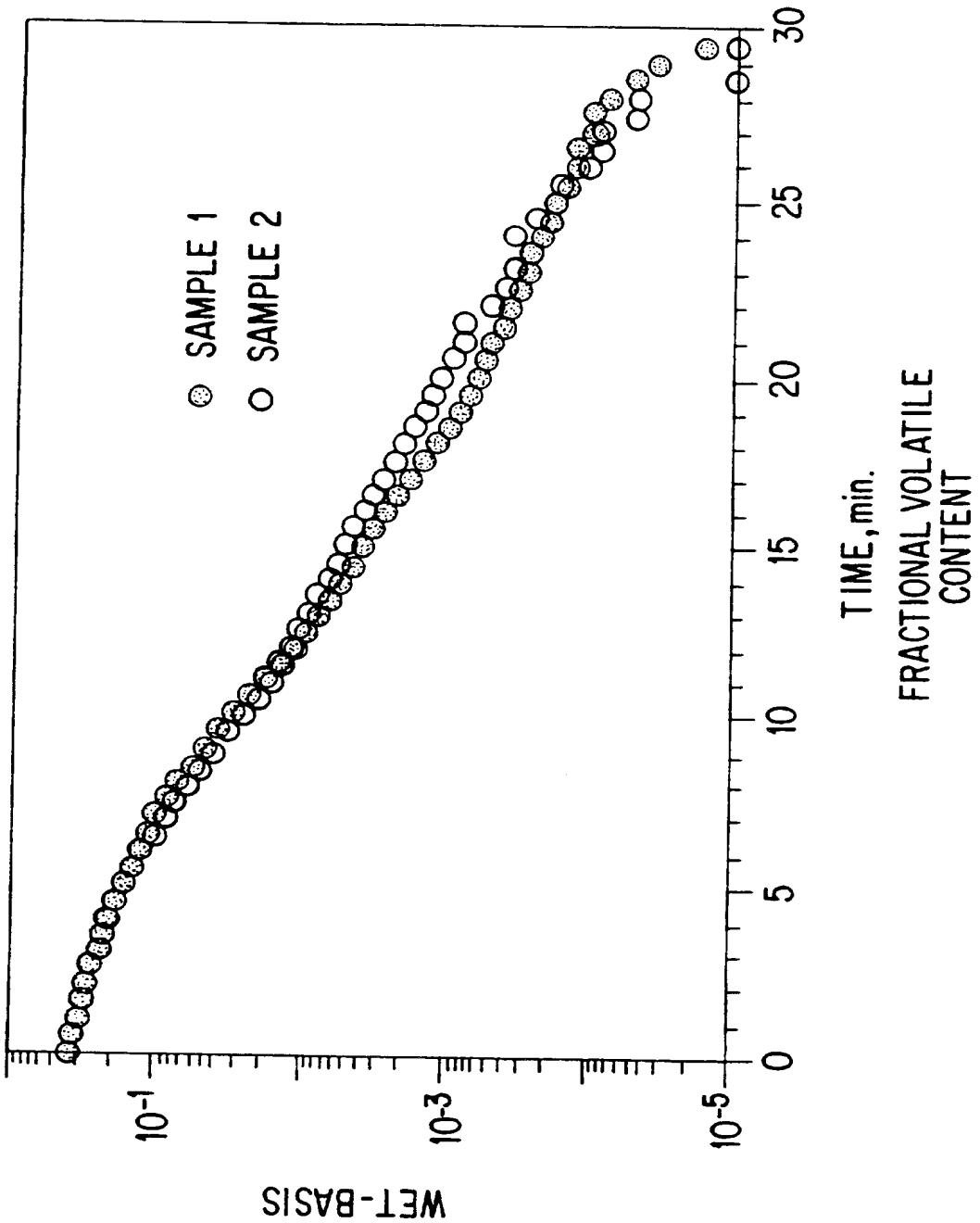
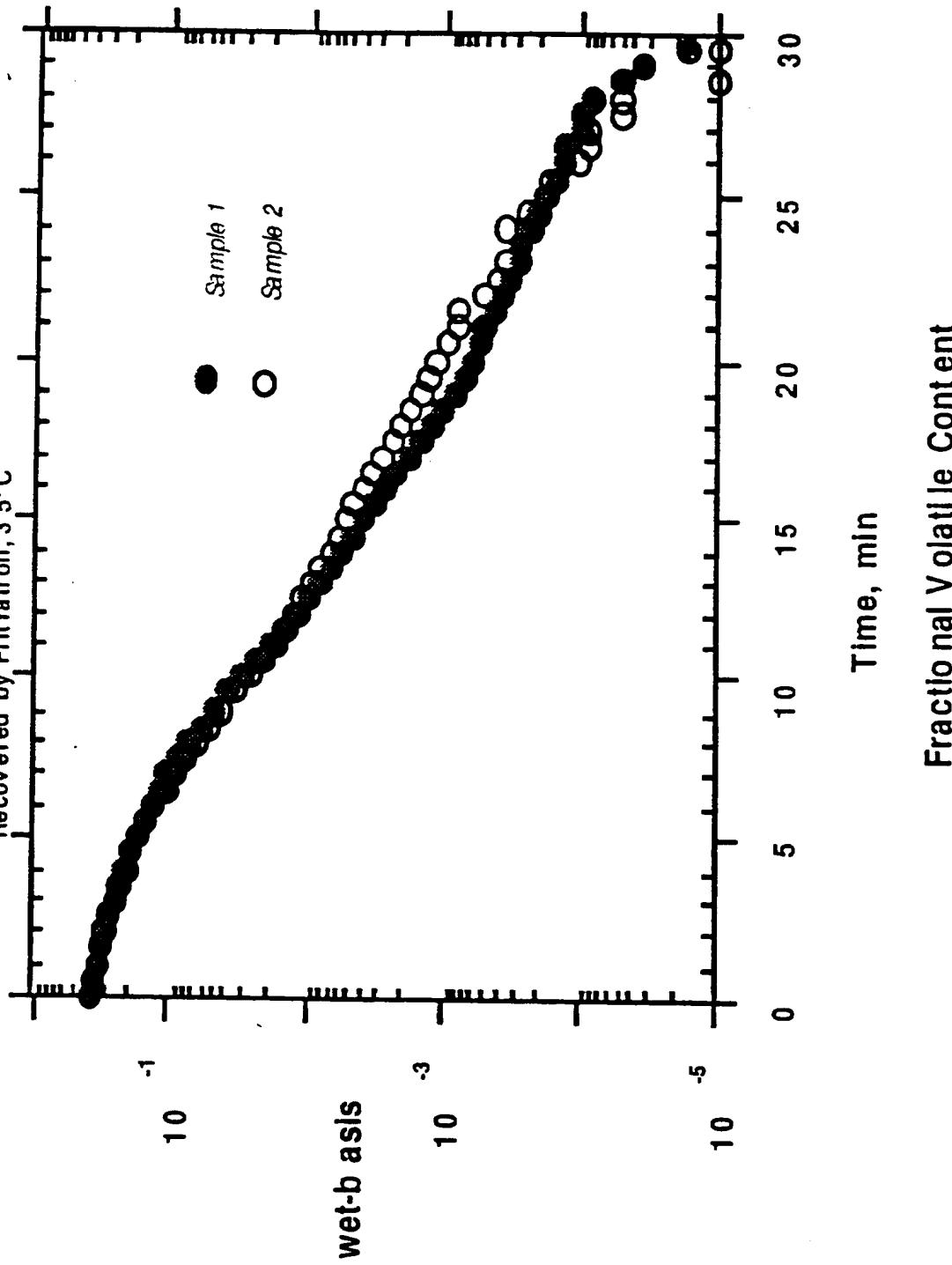


FIG. 1

FIGURE 1

Drying Curve of Microspheres
Recovered by Filtration, 35°C

2/2



Fractional Volatile Content

TITLE OF THE INVENTION

PROCESS FOR REMOVING ORGANIC PHASE SOLVENT FROM
PLGA MICROSPHERES CONTAINING A LIPOPHILIC DRUG

5 BACKGROUND OF THE INVENTION

The present invention relates to a process of removing the organic solvent from PLGA microspheres. Microspheres made of poly(lactide-co-glycolide) have been widely studied for the delivery of drugs and biologicals. One of the most popular methods for preparing 10 drug-containing microspheres involves the formation of an oil-in-water emulsion followed by solvent removal via an extraction/evaporation, henceforth referred to as the 'single emulsion process'. In this process, the suspension (after solvent extraction/evaporation and washing) is sometimes lyophilized with appropriate additives and packaged as a 15 finished product. More often, wet microspheres are recovered from the suspension, dried and packaged.

Ordinarily an extended solvent extraction step followed by 20 drying or other measures is required to provide PLGA microspheres which are suitable for use in pharmaceutical preparations. The present invention involves a minimum amount of organic solvent removal or extraction time, with up to about 95% removal occurring essentially in a few minutes.

SUMMARY OF THE INVENTION

25 In one aspect of the invention, a process for removing the organic phase solvent from poly(lactide-co-glycolide) microspheres containing a lipophilic drug compound is disclosed. The process comprises:

30 forming poly(lactide-co-glycolide) microspheres in an ethyl acetate/water two phase system;

emulsifying the two phase system at approximately a 1:1 to about 3:1 ratio of water to ethyl acetate continuously to form microspheres;

and continuously introducing the emulsion into a water reservoir which is less than about 15-20 times the volume of the cumulative volume of the emulsion, effective for extracting the ethyl acetate from the microspheres.

In a further aspect of the invention, the process is as described above, wherein the water reservoir is effective for extracting up to about 95% of the ethyl acetate from the microspheres.

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In yet another aspect of the invention, the process is as described above wherein the lipophilic drug compound is selected from the group consisting of: avermectins, milbemycins, nodulisporic acid and derivatives thereof, fipronil and steroids.

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BRIEF DESCRIPTION OF THE DRAWINGS

The invention is described in connection with the drawings appended hereto, of which:

20

Figure I is the isothermal drying curve of a wet microsphere cake.

DETAILED DESCRIPTION OF THE INVENTION

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The following terms and definitions are applicable to the invention described herein unless otherwise indicated:

30

As used herein, the term "poly(lactide-co-glycolide)" is used in the conventional sense to refer to: poly(glycolic acid), poly-d, l-lactic acid, poly-l-lactic acid, copolymers of glycolic acid, l-lactic acid and d,l-lactic acid. Commercial vendors include Medisorb Technologies International (MTI), Boehringer Ingelheim and Birmingham Polymers.

Lipophilic drugs which are useful in the present invention include the following: avermectins, milbemycins, nodulisporic acid and derivatives thereof, fipronil and steroids. Generally, lipophilic drugs

useful herein include those drugs which are water insoluble, and soluble in ethyl acetate and methylene chloride.

5 The emulsion that is continuously formed is introduced into a water reservoir as quickly as possible, preferably immediately. The water reservoir is up to about 15 to 20 times the cumulative volume of the emulsion.

10 Emulsifying agents which are useful in the present invention include: poly(vinyl alcohol), Tween 80, polysorbates and poloxamers.

15 The invention is further illustrated in connection with the following non-limiting example.

Materials

PLGA (8515, iv= 0.689 dL/g) was purchased from MTI (Cincinnati, OH). Ethyl acetate and poly(vinyl alcohol) (88% hydrolyzed were supplied by Aldrich.

Procedure

Avermectins (1 part) and PLGA (1 part) were dissolved in ethyl acetate (8 parts) to form the "organic phase". Poly(vinyl alcohol) was dissolved in water (0.5%) to form the "aqueous phase".

25 The two phases were mixed and emulsified continuously using an on-line static mixer at ~2:1 ratio (aqueous:organic) and the emulsion was introduced immediately into a water reservoir under gentle agitation. The water reservoir is up to about 15-20 times the cumulative volume of the emulsion and is maintained at approximately 10°C.

Extraction rate of ethyl acetate

Four batches of different sizes were made. The final ethyl acetate concentration in the water reservoir ranged from ~1.6 to ~5.0

wt%. As shown in Table 1, regardless of the batch size, approximately 90% of the solvent which was introduced via the oil-in-water emulsion was extracted into the water reservoir within 5 minutes. Longer extraction times removed marginally more solvent from the wet
5 microspheres.

Since the yield of dry microspheres was greater than 95%, the wt% of ethyl acetate in the wet microspheres can be estimated from the data in Table 1. The estimates are shown in Table 2. Roughly 30
10 wt% of the wet microspheres is attributed to residual ethyl acetate.

Drying characteristics of wet microspheres

The isothermal drying curve of the wet cake is illustrated in Figure 1. The TGA analysis was run at 35°C, with a dry-nitrogen flow
15 rate of 10~20- cc/min. The volatile content of the microspheres can be lowered to less than 1 wt% in less than 15 min.

The total volatile content of the wet microspheres can also be determined from the drying curve. These data are summarized in
20 Table 3. The volatile content does not vary much with extraction time.

Comparing the data in Tables 2 and 3 one also finds that more than two thirds of the volatile content of the wet microspheres is indeed solvent, the rest is water.

Table 1
Percent Solvent Extracted into Aqueous Phase After Dispersion

Time, min	Batch ID			
	A	B	C	D
5	91%	90%	90%	92%
15	88%	90%	90%	92%
60	87%	90%	96%	-
Average Solvent wt% in the Aqueous Phase	9.95	1.61	4.36	5.04

5

Table 2
Solvent content of wet microspheres recovered by filtration
(Calculated from solvent extraction data.)

Batch ID	A	B	C	D
% Wt (wet-basis)	30	30	29	23

10

Table 3
Volatile content of wet microspheres recovered
at various times after dispersion

15

Time, min	10	24	38	60
% Wt (wet-basis)	33	35	31	38

When ethyl acetate was used as the solvent for the preparation of microspheres in the 'single emulsion process', around 90% of the solvent was extracted into the water reservoir within 5 min.

20 Prolonging the extraction did not significantly increase the extent of solvent removal from the wet microspheres.

The high volatility of ethyl acetate, the small size of the microspheres (volume-average diameter in the range of 50 to 120 micron), and the favorable external mass transfer used allows nearly 5 complete drying of the microspheres (to <1 wt%) within 15 min at 35°C.

While certain preferred embodiments are described herein in detail, numerous alternative embodiments are contemplated as falling 10 within the invention.

WHAT IS CLAIMED IS:

5 1. A process for removing an organic phase solvent from poly(lactide-co-glycolide) microspheres containing a lipophilic drug compound, which comprises:

10 combining poly(lactide-co-glycolide) and a lipophilic drug compound in an ethyl acetate/water two phase system;

15 emulsifying the two phase system at approximately a 1:1 to about 3:1 ratio of water to ethyl acetate continuously to form microspheres;

20 15 and continuously introducing the emulsion into a water reservoir which is less than about 15-20 times the volume of the cumulative volume of the emulsion, effective for extracting the ethyl acetate from the microspheres.

25 2. A process in accordance with claim 1 wherein the water reservoir is effective for extracting up to about 95% of the ethyl acetate from the microspheres.

30 3. A process in accordance with claim 1 wherein the two phase system is emulsified at approximately a 2:1 ratio of water to ethyl acetate.

35 4. A process in accordance with claim 2 wherein the lipophilic drug compound is selected from the group consisting of: avermectins, milbemycins, nodulisporic acid or a derivative thereof, fipronil and steroids.

5. A process in accordance with claim 1 wherein said emulsifying is comprised of adding an emulsifying agent selected from the group consisting of: poly(vinyl alcohol), Tween 80, polysorbates and poloxamers.



The Patent Office

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Claims searched: 1-5

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Patents Act 1977 Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): A5B (BNC)

Int Cl (Ed.6): A61K 9/16

Other: ONLINE: WPI, CAPLUS

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X	WO 95/13799 A1 (MEDISORB. TECH. INT.) page 25 lines 21-26; Examples 6, 9, 10, 15 and 17	1, 4 & 5 at least
X	WO 95/11009 A1 (GENENTECH INC.) page 12 line 46-page 13 line 4	1 & 5 at least
X	Proc. Int. Symp. Controlled Bioact. Mater Vol. 23 1996. Chern R T <i>et al.</i> "Some observations on the solvent extraction and drying characteristics of PLGA microspheres". pages 363-364	1 & 5 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.